Two special histologic types frequently overexpress HER2. The tumor cells of **apocrine carcinoma** resemble the cells that line sweat glands. These cells have enlarged round nuclei with prominent nucleoli and abundant eosinophilic, occasionally granular, cytoplasm (Fig. 23-24*E*). **Micropapillary carcinoma** (a misnomer) forms hollow balls of cells that float within intercellular fluid, creating structures that mimic the appearance of true papillae (Fig. 23-24*F*).

ER-negative, HER2-negative tumors often correspond to one of several special histologic types. Chief among these is **medullary carcinoma**. Medullary carcinoma is softer than other carcinomas (*medulla* is Latin for "marrow") due to minimal desmoplasia, and often presents as a well-circumscribed mass. It is characterized by (1) solid, syncytium-like sheets of large cells with pleomorphic nuclei, and prominent nucleoli, which compose more than 75% of the tumor mass; (2) frequent mitotic figures; (3) a moderate to marked lymphoplasmacytic infiltrate surrounding and within the tumor; and (4) a pushing (noninfiltrative) border (Fig. 23-24*G*). DCIS is minimal or absent. Due to difficulties in defining this subtype, the current World Health Organization classification system recommends grouping medullary carcinomas with similar carcinomas into one group termed "carcinomas with medullary features."

Other ER-negative, HER2-negative special histologic types include secretory carcinoma, spindle cell carcinoma, low-grade adenosquamous carcinoma, and adenoid cystic carcinoma. **Secretory carcinoma** mimics lactating breast by forming dilated spaces filled with eosinophilic material (Fig. 23-24*H*).

Another clinical and morphologic subtype that merits brief mention is **inflammatory carcinoma**. As discussed earlier, these tumors show extensive invasion and proliferation within lymphatic channels, causing swelling that mimics non-neoplastic inflammatory lesions. These tumors are usually of high grade, but do not belong to any particular molecular subtype.

Male Breast Cancer

The incidence in breast cancer in men is only 1% of that in women, which translates to a lifetime risk of 0.11%. There are about 2000 cases and 400 deaths in the United States each year. Risk factors are similar to those in women and include increasing age, first-degree relatives with breast cancer, exposure to exogenous estrogens or ionizing radiation, infertility, obesity, prior benign breast disease, and residency in Western countries. From 3% to 8% of cases are associated with Klinefelter syndrome and decreased testicular function. The typical age at diagnosis is between 60 and 70 years. From 4% to 14% of cases in males are attributed to germline *BRCA2* mutations. There is a 60% to 76% chance of a *BRCA2* mutation in families with at least one affected male. Male breast cancer is also observed in *BRCA1* families, although not as frequently (Table 23-2).

The pathology of male breast cancer is remarkably similar to that of cancers seen in women. However, ER positivity is more common (81% of tumors). Prognostic factors are similar in men and women.

Because breast epithelium in men is limited to large ducts near the nipple, carcinomas usually present as a palpable subareolar mass, 2 to 3 cm in size and/or as nipple discharge. The carcinoma is situated close to the overlying skin and underlying thoracic wall, and even small carcinomas can invade these structures and cause ulceration. Dissemination follows the same pattern as in women, and axillary lymph node involvement is present in about half of cases at the time of diagnosis. Distant metastases to the lungs, brain, bone, and liver are common. Although men present at higher stages, prognosis is similar in men and women when they are matched stage for stage. Most cancers are treated locally with mastectomy and axillary node dissection. The same systemic treatment guidelines are used for men and women, and response rates are similar.

Prognostic and Predictive Factors

The outcome for women with breast cancer depends on the biologic features of the carcinoma (molecular or histologic type) and the extent to which the cancer has spread (stage) at the time of diagnosis. Many women with breast cancer have a normal life expectancy, whereas others have only a 10% chance of being alive in 5 years. Tumors that present with distant metastasis (<10% of breast cancer cases) or with inflammatory carcinoma (<5%) have a particularly poor prognosis. For all other women, prognosis is determined by pathologic examination of the primary carcinoma and the axillary lymph nodes.

Prognostic information is important in counseling patients about the likely outcome of their disease, choosing appropriate treatment, and the design of clinical trials. Prognostic factors fall into two groups—those related to the extent of carcinoma (tumor burden or stage) and those related to the underlying biology of the cancer. Prognostic factors related to extent of carcinoma are as follows:

- ***Invasive carcinoma versus carcinoma in situ.*** Women with in situ carcinoma understandably have an excellent prognosis. Only rarely do such patients die due to the subsequent development of invasive carcinoma or areas of invasion that were not detected at the time of diagnosis.
- ***Distant metastases.*** Once distant metastases are present, cure is unlikely, although long-term remissions and palliation can be achieved, especially in women with ER-positive tumors. As discussed earlier, the tumor type influences the timing and location of metastases (Table 23-3).
- ***Lymph node metastases.*** **Axillary lymph node status is the most important prognostic factor for invasive carcinoma in the absence of distant metastases.** The clinical assessment of lymph node status is unreliable due to both false positives (e.g., palpable reactive nodes) and false negatives (e.g., lymph nodes with small metastatic deposits). Therefore, biopsy is necessary for accurate assessment. With no nodal involvement, the 10-year disease-free survival rate is close to 70% to 80%; the rate falls to 35% to 40% with one to three positive nodes, and to 10% to 15% when more than 10 nodes are positive. Lymphatic vessels in most breast carcinomas drain first to one or two *sentinel nodes*, which can be identified with radiotracer or colored dyes. If a biopsy restricted to the sentinel nodes is negative for metastasis, it is unlikely that other more distant nodes will be involved and the patient can be spared the morbidity of a complete axillary dissection. Approximately 10% to 20% of women